THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MARCH, 1922

ORIGINAL ARTICLES.

RELATION OF ALEUKEMIC LEUKEMIA, SO-CALLED PSEUDOLEUKEMIA AND MALIGNANT GRANULOMA.

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THERE is perhaps no more unsatisfactorily classified subject in the scope of the medical sciences than the enlargements of lymphatic nodes, or the hyperplasias of allied tissues, in the absence of a definite increase of circulating leukocytes. These diseases have been subjected to intensive investigation rather spasmodically during the past fifty years, but recently a generally heightened interest has been evident. This may be due to the fact that these diseases have increased in incidence—more cases have been seen in the University Hospital in recent years—the stimulation of investigation originating from certain bacteriologic findings in lymphogranuloma and the newer work upon the reaction of lymphatic organs to light rays. Increased clinical experience has, however, demanded a classification which will fit in with clinical course, reaction to roentgen-ray treatment and probable result from such treatment.

This laboratory and clinic have joined in the study of the whole subject of leukemic and aleukemic adenopathy for several years, a coöperation which has brought to light several interesting cases and a few profitable facts. The present paper puts on record three cases, grouped by their age, clinical course, physical appearance and somewhat by their pathology, which were diagnosed as Hodgkin's disease at first, but by close clinical analysis were removed from this category, and by the examination of excised glands were placed among the tumors and leukemias, or so-called pseudoleukemia.

The term "pseudoleukemia" was coined by Cohnheim in 1865 to describe a case of generalized lymph-gland enlargement without a leukemic blood picture. Since Cohnheim's time the term has been misused by very many writers. In a very cursory examination of the literature for this purpose, including the International List of the Causes of Death, we have found nineteen names purporting to cover his conception. More than that it became the custom in Europe before Sternberg's publications in 1898 and 1905 to speak of nearly all lymph-gland tumors as pseudoleukemia, and the term was, in certain quarters, synonymous with Hodgkin's disease.

Despite Turk's request of 1899, Sternberg's presentation before the German Pathological Society in 1912 and Symmers's article in 1909, this synonymous use of the term for Hodgkin's disease has persisted in literature. Sufficient evidence, however, is at hand to warrant the discontinuation of the use of the term in Hodgkin's disease and is rapidly accumulating against its application to the aleukemic stages or forms of leukemia. Sternberg does not believe it necessary. Pathologically speaking—and it is upon bioscopical and necroscopical glandular pathology that one should base a diagnosis—there seems little justification to apply the term "false leukemia" to the aleukemic stages of leukemia. Sternberg's grouping of Banti's disease under this title has more justification than the inclusion of more definite glandular or myeloid pictures. This, however, is not our present problem. We believe that this term "pseudoleukemia" should be used in an adjectival sense only and that there are adequate names and pictures for the groups to which it has been collectively applied. Thus, for example, the following cases, while not presenting a typical leukemic blood picture, have some evidence of lymphoid-cell production and a type of adenopathy consistent with general diseases of the lymphatic system. Such a clinical state hardly needs the name false leukemia, especially when a gland removed during life showed lymphoid hyperplasia of the leukemic type.

Case I.—S. O., aged sixty years, m., w., s. Admitted to the University Hospital, December 4, 1920, complaining of swelling of the neck, axilla and groins. Had been in good health until April, 1919, when he noted a small swelling in the right axilla. A mass appeared a month later in the left submaxillary region. These masses probably increased but gave no trouble. In December, 1919, he began to have dyspnea, especially at night. The tonsils were then discovered to be large and diseased and were removed December 23, 1919. This removal cured his dyspneic symptoms. When the glands were first noticed the patient believes that his voice became weaker, although at times it seemed normal. The patient was in good condition, without much change in glands, until June, 1920, when after a slight cold masses began to enlarge. All his teeth except eight front lower teeth were removed, after which some of the glands decreased somewhat. He remained in fair condition, but noted that he was tired and was going down hill when he was admitted in December, 1920. Lost twenty pounds in two years.

The previous medical history shows diseases of childhood with permanent impairment of hearing due to scarlatina. Had pneumonia when young and again when sixteen. Social and family history are negative.

Physical examination showed a well-nourished man with soft dry skin except over the knees and elbows, where it was wrinkled and harsh. The neck was the same width as the head, due to enlargement of lymph nodes. The mouth and pharyngeal cavity were negative. The remaining teeth were in fair condition. The pharynx and the remaining lymphadenoid tissue were congested. The neck, both anteriorly and posteriorly, showed irregular masses from pea to egg size, discrete, sharply outlined, freely movable, not adherent to skin. The thyroid was not enlarged; there was no tracheal tug. Chest emphysematous. Several masses under the skin similar to those in the neck. The axillary fossæ were filled with enlarged masses like in the neck. Lungs were negative. Heart area was enlarged to the left in the second interspace. L. B., 13 cm.; R. B., 3.5 cm.; L. O., 16 cm.; R. O., 9. cm.; in the first interspace, 8 cm. wide. There was some peripheral arteriosclerosis. Blood-pressure, 140–90.

The abdomen had a fatty flaccid wall except the upper section of the recti, which was resistant, and gave the impression of a mass beneath. The liver extended from the fourth costal space to the rib margin. The spleen was not palpable. The inguinal glands were enlarged like those in the axilla. The right epitrochlear gland was palpable. The patient was allowed to go out for a couple of weeks to return for roentgen-ray treatment. He worked rather hard and there was an enlargement in his glands during his absence. Before his temporary discharge a gland was removed under local anesthesia and was diagnosed as leukemic hyperplasia and not Hodgkin's disease, which was the preliminary diagnosis. The patient received very little treatment aside from the roentgen-ray, sodium cacodylate, $\frac{1}{4}$ grain, being the only important measure used during his twelve days of treatment. There was a slight decrease in the size of the glands, but they did not become firmer. Following exposure while going to the roentgen-ray he developed lobar pneumonia at the left base and died. Before the development of this infection his temperature had ranged between 97° and 99° F., with a relatively higher pulse and respiration rate. During the pneumonia the rates were proportionate. The urine had shown a specific gravity from 1016 to 1020, with a constant trace of albumin and a few hyaline and light granular casts. Intake and output were proportionate. The phthalein elimination was 60 per cent. The skin tests for tuberculosis were negative. The Wassermann was negative.

Blood counts:

Hgb.	R.B.C.	W.B.C.	P.	L.	M.	Tr.	E.	B.
88	4,070,000	5900	54	38	6	1	4	
93	5,400,000	6500	52	40	3	3	1	1
Roentgen-ray started:								
87	4,300,000	5900	56	37	5	2		
85	4,450,000	6100	74	20	3	3		
		3300	64	33	1	2		
92	4,700,000	6600	56	36	4	2	..	2
Pneumonia:								
85	4,400,000	6100	74	20	3	3		
		3300	64	33	1	2		

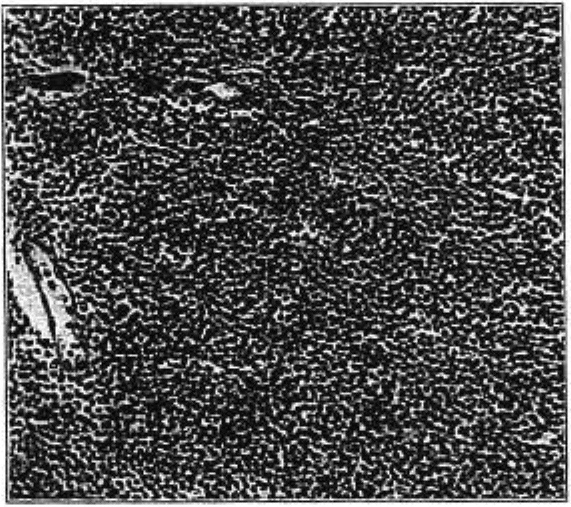

FIG. 1.—552. S. O. Uniform hyperplasia of lymph node diagnosed as leukemic hyperplasia; case aleukemic. Cells 7 to 10 microns. Compare with Case II, Fig. II, and A. H., Fig. IV, but contrast with A. E., lymphogranuloma, Fig. III.

A gland from the neck was about 2.5 x 2 cm. The smooth pale pink capsule is thin and uniform on section. The mass is pale, gray-pink, homogeneous, soft and not traversed by fibrous bands. Section (Fig. 1) consists of a rather uniformly staining mass fairly well outlined by a delicate capsule, outside of and within the splits of which are cellular infiltrates. The marginal sinus cannot be recognized but the arrangement of some of these infiltrates raised the question as to occupation of what was the marginal sinus. The tissue cannot be recognized as lymph node. It seems to be made of a single type of cell separated by a few delicate connective-tissue strands carrying bloodvessels and cut at different angles. The cells vary from 7 to 11 microns, the nuclei from 5 to 9 microns. The nuclei are fairly well stained and have a clear but delicate nuclear network. The protoplasm is neutrophilic with here and there a slightly oxyphilic example. They are mostly round or elliptical, but some compressed ones are seen. Here and there one will see what seem to be a true young connective-tissue nucleus.

By Van Gieson the capsule and delicate septa show clearly, but there are no fibers between the cells.

A polychrome stain (only fairly satisfactory) shows no true granules of the myeloid type, but here and there one finds pictures like azure granules. By this stain a polynuclear eosinophile was seen and large mononuclears of large endotheliocyte proportions were found, and these have distinct vesicular nuclei and a purple cytoplasm, very distinct from the scanty neutrophilic protoplasm of the average cell of the section. One eosinophilic mononuclear was found.

The Schridde stain reveals no real perinuclear granules. Here and there one sees masses of irregular staining and granulated appearance and also masses of matter which might correspond to the abovementioned azure granules. Section shows no oxidase granules by Graham's method.

Clinical Diagnosis. Aleukemic lymphatic leukemia.

Bacteriologic Diagnosis. Cultures: Heart blood; mesenteric lymph node negative.

POSTMORTEM.

Gross Anatomical Diagnosis.	*Histological Diagnosis.*
Lymphatic leukemia.	
Aorta: Early atheroma.	
Heart: Dilatation; fibrosis of the myocardium; subacute verrucose endocarditis of mitral valve.	Old healed myocarditis; acute infectious mitral valvulitis with vegetation.
Left lung: Acute fibrinous pleurisy; lobar pneumonia; beginning consolidation of the lower lobe.	Croupous pneumonia.
Right lung: Obliterative pleurisy; hypostatic congestion and edema.	Hemorrhage.
Spleen: Lymphatic leukemia.	Endothelial and lymphoid hyperplasia; congestion.
Stomach: Congestion and submucous hemorrhages.	Petechial hemorrhages.
Liver: Lymphoid infiltration.	Lymphoid infiltration; cloudy swelling; fatty infiltration.
Leukemic tumor of retroperitoneal tissue.	
Kidneys: Slight chronic interstitial nephritis; cloudy swelling.	Chronic interstitial nephritis; cloudy swelling; lymphoid infiltration.
Bladder: Distention.	
Pancreas:	Normal.
Lymph node:	Lymphatic leukemia.

EXTERNAL EXAMINATION. Autopsy one hour after death. Body of white male, aged fifty-eight years, looks not over fifty; 172 cm. in length, weighing about 160 pounds; of normal framework and good nutrition. Rigor not yet established; *livor mortis* present. Skin is smooth except for a slight healed scar over the left mandible. There is general glandular enlargement, involving especially the auricular, maxillary, cervical, axillary and inguinal nodes. These are soft and feel distinct. The skull is normal. The pupils equal and regular. The scleræ are clear. The nose and ears are negative. Many teeth are missing. The neck appears fat. The thorax is well developed. The genitalia are normal. A number of spots are seen about the right nipple, suggesting puncture wounds. The extremities are negative and the hair distribution is normal.

INTERNAL EXAMINATION. *Thorax.* The left pleural cavity is free from adhesions and fluid. The right pleural cavity is obliterated by dense adhesions. The pericardial sac is normal.

Aorta. The aorta is of normal caliber and shows numerous gray-yellow plaques in all portions.

Heart. Weighs 300 gm.; the epicardium is smooth without excess of fat. The organ is firm. The myocardium is dark brown with fibrous streaks. The papillary muscles and the chordæ tendineæ are normal. The mural endocardium everywhere is thin and smooth. The bases of the aortic cusps are slightly stiffened. On the auricular surface of the mitral valve is a group of small, rather soft, wart-like, yellowish growths. Other leaflets are delicate. The wall of the left ventricle is 16 mm.; right, 3 mm. The aortic orifices, 7 cm. Both ventricles are moderately dilated. The coronary artery is not sclerosed. The trachea and bronchi show no changes. The mediastinal lymph nodes are much enlarged, gray, soft and discrete.

Left Lung. Weighs 900 gm.; upper lobe is consolidated, except for the anterior margin. The lower lobe is crepitate, except for a small area posteriorly. The pleura of the upper lobe is covered with a little fresh fibrin. There are no apical scars. The cut surface of the upper lobe is gray, granular, slightly moist and airless; of the lower lobe red and moist; air can be expressed, except in a small patch posteriorly; bits of tissue of this area float in water. The peribronchial lymph nodes resemble those already described.

Right Lung. Weighs 500 gm.; normally collapsed. Cut surface is red and moist, and contains air, except for a dark red, hemorrhagic-looking area in the posterior part of the lower lobe. Pieces from this sink in water.

Abdomen. The abdominal fat, 1½ cm., flabby and moist looking. Muscles flabby, and this is true of the general musculature. The peritoneum is smooth, glistening and free from adhesions. There is no fluid in the peritoneal cavity. The bladder is much distended. The diaphragm reaches the fourth rib on the right side and the fifth on the left.

Spleen. Weighs 280 gm.; firm and capsule is smooth. The cut surface is dark red; the trabeculæ are indistinct. The follicles are greatly enlarged and white. There are several larger white areas about 3 mm. in diameter.

Stomach. The stomach is moderately distended. The mucosa is normally rugous, showing numerous petechial hemorrhages.

Intestine. The intestine is negative. The bile passages are patulous.

Liver. The liver was not weighed, but probably weighed about 2000 gm., 29 x 23 x 10 cm., and of normal consistency. The lower border is somewhat rounded. The capsule is transparent. The cut surface is gray with distinct red centers of lobules; the surface is even.

Pancreas. Is small, of normal consistency and normally lobulated. Close to the pancreas is a tumor-like mass, 13½ cm. in greatest dimension. This is encephaloid, gray but not lobulated. Besides the main mass are many small, similar nodes, apparently enlarged lymph glands. Similar brain-like tissue is found along the abdominal aorta, forming practically a sheet of new growth throughout the retroperitoneal tissue. This growth is lobulated, and similar to glands of the neck, which had been exposed to roentgen-ray treatment,

Left Kidney. Weighs 230 gm.; 14 x 6 x 5 cm.; of normal consistency. Capsule strips with difficulty, leaving a pink, granular surface with a few scars. The cut surface is generally gray with bulging edges. Cortical striations are indistinct; those of the medulla appear normal. The glomeruli are of usual size. The pelvis is distended. The peripelvic fat is moderately increased.

Right Kidney. Weighs 170 gm.; 14 x 5 x 5 cm.; cortex, 7 mm.; medulla, 15 mm.; otherwise resembles its fellow.

The vertebral column, ureters, urinary bladder, prostate, seminal vesicles and psoas muscle are negative.

Notes: The bone-marrow of the shaft of the femur is red; that of the ribs shows no changes.

MICROSCOPICAL. *Heart.* The epicardium is of the usual thickness but shows no vascular or other changes. The endocardium is not shown. The myocardium shows very extensive replacement of the muscle, with fibrous tissue of adult type, in the midst of which, here and there, muscle fibers persist. From this last point and from the irregular outline the lesion appears not to be a healed infarct. There is no cellular infiltration or vascular change. Uninvolved muscle fibers are of the usual size, with preserved cross-striations, well-staining nuclei and inconspicuous peripolar pigment. The second section is from the mitral valve. The tissue consists of adult connective-tissue without bloodvessels, except in one area in which there are leukocytes and mononuclear cells. On the surface of the leaflet, corresponding to this area of infiltration, is a hyaline blood-clot in which are numerous areas of softening containing innumerable bacteria. The edge of the clot blends with the margin of the leaflet.

There is no apparent invasion of the leaflet by bacteria, nor any organization of the clot.

Left Lung. The pleura is much thickened with adult fibrous tissue, the superficial layer being heavily infiltrated with lymphocytes. The pulmonary tissue is uniformly consolidated, the exudate consisting of fibrin, leukocytes and with vast numbers of bacteria and a few red cells. Capillaries are compressed by the exudate. The interstitial tissue and vessels show no change.

Right Lung. The pleura is absent. The pulmonary tissue is uniformly consolidated with red blood cells, with which are a few leukocytes but no fibrin. Alveolar walls, capillaries and interstitial tissues show no changes.

Spleen. Capsule and trabeculæ are normal. Follicles are greatly enlarged, with hyperplasia of lymphoid cells and the presence of coarse reticulum. The pulp is very bloody. There is one area of extensive endothelial hyperplasia. These endothelial cells are supported on a rather coarse reticulum, and are mixed with lymphocytes and leukocytes. There is not, however, diffuse endothelial hyperplasia through the pulp.

Stomach. Only mucosa and submucosa are shown. The former shows many hemorrhagic points but no exudative features.

Liver. The capsule is normal. Extensive lymphoid infiltration is found in the perilobular tissue, which is greatly widened; in these areas the bile ducts appear to be increased numerically. The liver cells are large, crowding the capillaries; they are granular, and nuclei often are poorly seen. Many rather small vacuoles are present, becoming rather large in the peripheral zone. The central veins are not distended. No fibrosis is seen.

Pancreas. The interstitial tissue is normal, as are the vessels and the ducts. The islets are numerous and large; the acini show no changes.

Kidney. The capsule is infiltrated with lymphoid cells. The interstitial tissue is much increased as streaks in the cortex, associated with hyalinization of many glomeruli and compression of tubules. Elsewhere tubules are of full size, with somewhat swollen, ragged and granular cells, in which nuclei are faint. No definite vascular lesions are seen, except for perivascular lymphoid infiltration.

Lymph Node. Follicles and sinus arrangement are completely obliterated. The structure consists of lymphoid cells supported on a reticulum.

There are numerous small bloodvessels. This tissue freely extends beyond the capsule.

Two additional sections show the same feature, with infiltration of the capsule by lymphoid cells.

CASE II.—J. M., aged sixty-one years, w., m., s. Admitted to the University Hospital for nodules on each side of the neck, in the axilla and in the inguinal regions. He has been in fair health until two years ago, when he noticed the small lumps on the right side of the neck about the size of a pea, which were followed by others. These were firm, discrete and without discomfort. They grew steadily, and two months later similar masses appeared in the axillæ and the groins. They were all of the same character. Has had some carious teeth but paid no attention to them. No loss of weight and no history pointing to any organic lesion. His previous medical history was negative until he had influenza, September, 1918, at which time the masses in the neck increased in size. In December, 1919, he had a second attack of influenza, with intestinal symptoms. On January 20, 1920, had acute pleurisy, after which he did not work until his admission to the hospital in March, 1920. The latter illnesses had no effect on the glands. He was a ship and stationary engineer. His personal and family history are negative.

A physical examination in the hospital shows a well-developed large male, tending to fatness, and appearing well except for the general adenopathy. Blood-pressure, 122–90. The teeth are dirty and carious, and considerable pyorrhea exists. Has some chronic pharyngitis. The neck is short and thick, with bilateral swellings from the jaw to the clavicle anteriorly and posteriorly. The masses vary greatly in size, pea to walnut—discrete, freely movable, firm, smooth but not tender or painful. No adhesion to the skin. No tracheal tug. The chest is large and emphysematous. Glandular masses are found below the clavicle and extending in the anterior axillary region. The left chest is more prominent than the right, the expansion being limited on both sides; the percussion note is slightly impaired over the whole upper chest anteriorly and posteriorly. The breath sounds in this area are coarse and loud; there is a friction rub on the left base posteriorly. There are glandular masses above the spine of the scapulæ. The heart apex-beat is not seen or felt. The supracardiac dulness at the first interspace is 8 cm., second 6.5 cm., left base 12 cm.; right base 4 cm.; L. O., 20 cm.; R. O., 17 cm. The heart sounds are negative. The abdomen is full. Liver dulness over the sixth rib. The spleen comes below the costal margin only upon inspiration. Throughout the abdomen one gets the impression of numerous small masses beneath the skin or the abdominal wall. On the left side below the spleen and almost to the groin there is a resilient mass deep in the abdomen, probably retroperitoneal. On the right side there is definite resistance but no definite mass. Marked adenopathy in both axillæ, especially along the axillary folds, the individual ones being larger than in the neck. Masses in the groins are similar. No edema of extremities.

A gland was removed and diagnosed as not Hodgkin's disease or tuberculosis, but either sarcoma or leukemia, of which the latter was more probable because of the absence of intercellular fibers. The patient after exposure developed a lobar pneumonia of the right base and died. An autopsy was not permitted. The urinary examination showed the specific gravity ranging between 1020 and 1024, and an almost constant trace of albumin but no casts. The phthalein elimination was 55 per cent. The blood Wassermann was negative.

Blood counts:

Hgb.	R.B.C.	W.B.C.	P.	Small.	M.	Tr.	E.
82	4,800,000	13,800	43	36	11	7	3
	4,810,000	28,800	77	16 .	6	1	

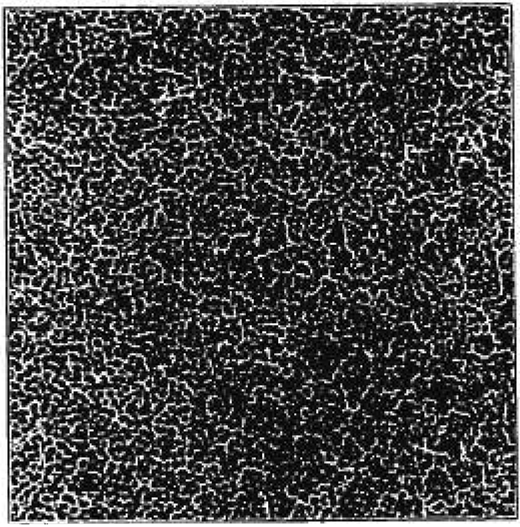

Fig. 2.—442. J. M. Uniform hyperplasia of lymph node without leukemia. Cells of 7 microns. Deeply staining nucleus. Diagnosed as aleukemic leukemia. Compare with Fig. I, Case I. and with A. H., Fig. IV, but contrast with Fig. III, A. E., lymphogranuloma.

The temperature ranged between 98° and 99° F. until the pneumonia developed, after which it developed 103° F.

Further detailed study of the excised gland revealed the following (Fig. 2): The specimen consists of a well-outlined cellular mass which cannot be positively recognized as a lymph node. The capsule is made up of dense fibers, a few long pale nuclei, and in the rifts columns of adult lymphocytes may be seen. The position of the marginal sinus is sometimes indicated by a rift containing a few pale cells and a few lymphocytes. Trabeculæ do not exist as in the normal gland. There are small irregular septa carrying bloodvessels. The extreme border under the capsule consists of small lymphocytes, of about 7 microns, rather uniformally packed. Between these cells, here and there, is a slightly swollen reticulum cell or a delicate connective-tissue septum. As one goes inward toward the center of the mass the cells retain their rather uniform solid closely packed arrangement and incomplete separation by stroma but become distinctly larger. Under magnification of 1200 they are found to consist of a nucleus with a moderately coarse skein, a nucleolus or two nucleoli, sharply outlined, and a small amount of granuloid neutrophilic protoplasm. Mitoses, apparently normal in character, are common.

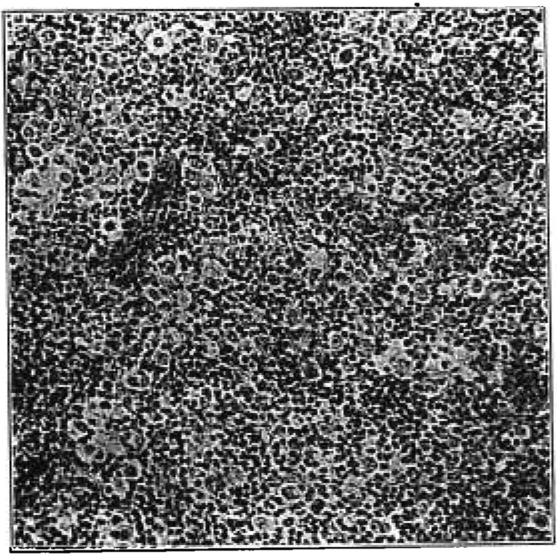

FIG. 3.—514. A. E. Hodgkin's disease in the cellular stage, six months' duration. Active process but the patient in reasonable good health and doing well under treatment.

By Van Gieson there is no stroma except the well-formed adult septa mentioned above. No endothelial, plasma, mast, eosinophile, neutrophile or giant cells. No fibrin, necroses, tubercles or pigment. The predominating type of cells is similar to some of the promyelocytes.

The Schridde stain fails to show any granulation in the protoplasm of the cells of this mass.

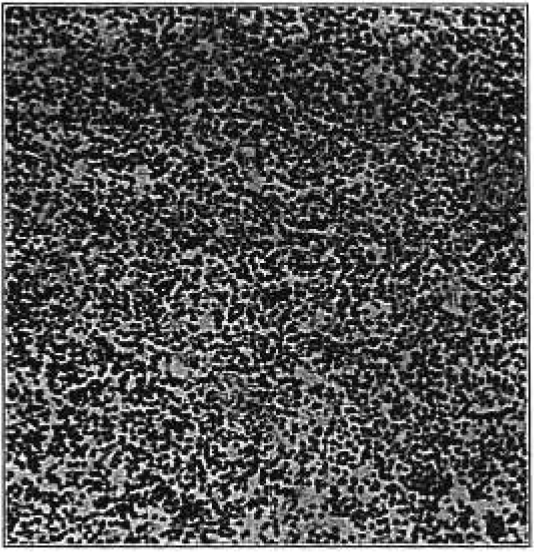

FIG. 4.—402-2 A. H. Axillary lymph node from a case of chronic lymphatic leukemia dying from pneumonia. Loose hyperplasia with much vascularization. Cells 7 to 8 microns.

CASE III.—S. J. M., aged sixty-one years, m., w. Admitted to the University Hospital February 14, 1914, complaining of swellings under the arms and in the neck and dyspnea. The patient has been in generally good health until six months ago, except four years before admission he had a swelling about the right elbow; this disappeared. Six months ago a lump appeared in the right axilla, which grew rapidly and became tender. Three months ago he had a swelling in the neck. He had a similar swelling on the left side. These swellings are slightly painful, sometimes extending down the arm, which is swollen; they are somewhat tender and have fluctuated in size. Sometimes one mass will enlarge while the other is smaller. None has broken down. Five months ago the patient began to have dyspnea and swelling of the feet; has had some palpitation, also dull pain across the chest, especially in the right mammary region. Had nocturia for three years. Had a chronic cough for fifteen years. When the glands first appeared he lost fifteen pounds, but since has gained and is now twenty-five pounds above weight.

The medical and social history are negative. His wife died of tuberculosis sixteen years ago.

The physical examination shows a heavily built, fat, florid, slightly dyspneic man between fifty and sixty. The muscles are flabby, the skin is warm and slightly yellowish. The superficial glands seem enlarged—solid, conglomerate and tender. They are fixed to the fascia but not to the skin. The axillary are most markedly involved, those in the neck and groins being smaller and more separate. The head and eyes are negative. The teeth are badly decayed and worn down; some pyorrhea The thorax is heavy. The right mammary and pectoral regions are indurated and tender with discolored skin over them. There is some impairment of resonance and bronchovesicular breathing at both apices anteriorly. Impairment of resonance and breath sounds over the whole right chest posteriorly. The apex impulse is not found. L. B., 13 cm., R. B., 5 cm.; L. O., 17 cm.; R. O., 15 cm. A blowing systolic murmur is heard at the apex and in the left axilla. The abdomen is large and pendulous. Liver 4 cm. below the umbilicus. The spleen is not felt. The extremities are negative except for a slight edema. The patient remained in this condition for several days, when he suddenly became toxemic and died in three days. For five days after admission he had run a temperature from normal to 101° F. It then settled to an irregular form, 97° to 100° F, with a disproportionately high pulse and respiration, and then continued until his toxemia appeared, when it became very irregular and up to 105°. A gland was removed and diagnosed as sarcoma, with reservation. The urine showed specific gravity of 1025, with a constant trace of albumin, and light granular casts. The Wassermann and von Pirquet were negative. A blood culture during the toxemic stage showed pneumococcus.

Blood picture:

Hgb.	R.B.C.	W.B.C.	P.	L.	M.	Tr.	E.	B.
86	4,400,000	9800	86	11	2			
84	4,900,000	9000	75	23	2			
89	5,100,000	22000	86	17	3	3	1	

A gland was excised during the treatment. No attempt was made to diagnose the original site of the growth, and at autopsy such an attempt failed.

Excised Gland. The material consists of several small fibrocellular pieces. The mass cannot be recognized as a lymph node. It has probably been partly encapsulated and spread out into and through the capsule. The capsule is wide, rather acellular; in its outer two-thirds it is adult fibrous tissue. The inner part is actively growing and consists chiefly of large elliptical or elongated, palely staining connective-tissue cells with a few small mononuclears, here and there a plasma cell, numerous in bloodvessels, a few free red blood cells—in other words, fairly active granulation tissue. There are rifts in and under the capsule filled with large cells to be described later. The majority of the mass consists of eosin-stained cell shadows and some better retained areas, with indefinitely stained basophilic nuclei. The center is difficult to describe and determine, but apparently the further one goes from the capsule the more there is disintegration; the remnants of fibers and long slender nuclei are to be seen irregularly scattered through the mass. It has apparently been very bloody, because there are some spaces filled with red blood cells apparently without wall and a few degenerated capillaries are seen. The cellular nests in the capsule consist of well-outlined groups of large cells with large well-outlined round elliptical and lobed nuclei and a small amount slightly granular or vacuolated protoplasm. There are sometimes several nuclei. The mitoses are moderately active. Red blood cells are numerous between these large cells. There are occasional polymorphous neutrophiles and eosinophiles. The cells of the central necrotic mass seem to have been the same kind of cells. Within the mass there are no lymphocytes and no endothelial, plasma or mast cells; a very vague reticulum is seen by Van Gieson; there are no eosinophiles; no myeloid or giant cells; no tubercles or pigment.

POSTMORTEM.

Gross Anatomical Diagnosis.	*Histological Diagnosis.*
Lymphadenitis of the axillary, subclavicular, subclavian, submaxillary and mediastinal lymph nodes.	Large round-cell sarcoma resembling lymph-node endothelioma.
Lung: Pleural effusion; healed pulmonary tuberculosis.	Emphysema, with secondary compression; atelectasis; passive congestion and chronic interstitial pneumonitis; chronic catarrhal bronchitis.
Heart: Pericardial effusion; fatty infiltration of the epicardium; cardiac hypertrophy; chronic fibrous aortic and mitral valvulitis; tricuspid and pulmonary insufficiency; right dilatation; chronic fibrous myocarditis; brown atrophy.	Chronic interstitial mural endocarditis; coronary sclerosis, with hypertrophy and secondary brown atrophy.
Liver: Cloudy swelling and fatty degeneration.	Passive congestion with parenchymatous degeneration and fatty metamorphosis.
Spleen: Chronic fibrous and calcareous capsular splenitis, with softening of the organ.	Chronic fibrous capsulitis.
Adrenals: Softening.	
Kidney: Chronic parenchymatous nephritis.	Congestion and cloudy swelling.
Stomach: Atrophic catarrhal gastritis.	
Fibrous and fatty endoaortitis of the aorta.	Chronic fibrous and fatty endarteritis.
Pancreas:	Atrophy, with replacement by fat.
Intestine: Meckel's diverticulum.	

Bacteriological Diagnosis. Streptococcus in cultures from heart blood, lung, spleen, liver, kidney and lymph nodes of the neck.

GENERAL. The body is that of an adult white male, aged fifty-five years; five feet eight inches tall; weighs about 200 pounds; is broad and thick-set, with a tendency to obesity; gray hair; blue eyes. The pupils are moderately dilated; the conjunctiva is muddy. Mouth: Teeth are in bad condition, especially the upper jaw, where only a few decayed ends are present. Mucous membranes are pallid. Both sides of the neck are swollen. Upon palpation the swelling is apparently in the cellular tissue as well as in the glands. There is a short, recently healed incision beneath the right ear. Rigor mortis is marked. Livor mortis in the dependent positions is marked over the anterior chest and over the neck. The tissues of both axillæ, but more especially the right side and the right flank, are boggy. There are well-marked palpable masses confined to the right axilla.

On primary incision the panniculus is found to be moderate; the musculature is fairly well developed. The axillary space was dissected out and contains an infiltrating mass of lymph nodes. These lymph nodes vary in size upon section from 4 cm. to 1 cm. They tend to run together, but the larger ones are sharply defined. Upon section they have a fleshy, firm appearance while some of the smaller ones have undergone a yellowish softening, which is comparable exactly in appearance to that of a mushroom which has its outer covering stripped off. Along the fascia of the pectoral muscle on the right side are numerous small bodies 0.5 cm. long, firm and fleshy; these do not infiltrate the muscle but seem to run somewhat into the fatty tissue over the pectoral fascia. This condition is not noted on the left side. The same small bodies are noted deep in the axilla and along the neck. The glands of the neck are enlarged in the same fashion, and upon section show caseous centers.

Abdomen. The cavity contains no fluid and the epiploic appendages are prominent. The lower border of the liver is at the border of the ribs. The stomach is slightly distended below this. The transverse colon, freely movable, runs straight across the abdomen. The great omentum is filled with an excessive amount of fat.

Liver. Weighs 2100 gm.; it measures 29 x 19 x 11 cm.; is pallid upon the surface and the edges are rounded; cuts with a buttery resistance. The cut surface is pallid, and the lobules are poorly defined. About the vessels may be seen radiations considered as fibrous. Some grease may be scraped from the surface. The gall-bladder contains 30 cc of a very dark viscid bile. The bile ducts are patulous.

Spleen. Weighs 300 gm.; measures 13 x 9 x 6 cm.; the organ is soft; the capsule is distinctly thickened and calcareous in some parts. The cut surface of the pulp is soft and mushy; the trabeculæ are moderately prominent, as are also the follicles. The surface has a generally pallid appearance.

Pancreas. Measures 20 cm.; long and is somewhat thinner than usual. Upon section the lobules are small and sharply defined.

Adrenals. Are small, friable and removed with difficulty.

Left Kidney. Weighs 230 gm.; measures 13 x 5 x 5 cm.; the organ is firm, pale, blue and cuts with resistance. The cut surface bulges. The capsule strips without difficulty leaving a smooth surface. The entire kidney substance measures 2.5 cm.; cortex, 6 mm.; surface is pallid with granular reddish interlineations following the course of the bloodvessels throughout the cortex.

Right Kidney. Weighs 190 gm.; measures 11.5 x 4.5 x 2.5 cm.; entire kidney substance, 3.5 cm.; cortex, 7 mm.; corresponds in detail to its fellow.

Bladder. Contains 1 dram of a light amber urine, but otherwise is negative.

Stomach. Contains about 200 cc of a liquid greenish content; distended with gas; flattens out readily upon the table. The wall is somewhat thinner than usual; mucosal surface is granular and thin.

Small Intestines. Shows a Meckel's diverticulum, otherwise nothing to note.

Thorax. The left pleural cavity is free from fluid and adhesions. The right pleural cavity contains 1000 cc of a serous fluid, non-inflammatory.

Right Lung. Weighs 285 gm.; floats upon the fluid and is collapsed; when cut it presents the exact appearance of its fellow on the opposite side. The basal portion of this lung shows some firm stony bodies which upon section seem to have a caseous center. Upon section the smaller bronchi purulent material exuded from each.

Left Lung. Weighs 350 gm.; upon removal it collapses and crepitates with a doughy feel. A very small area at the base is somewhat darker, otherwise the surface is pale gray, smooth and glistening. The organ cuts with resistance simply because the lung is difficult to hold. The cut surface is gray and dry; at the base a small amount of fluid exudes. The mediastinal lymph nodes, bronchi and trachea were removed in one mass. The trachea has an excess of mucus; it is small and shows considerable injection.

Heart. Weighs 440 gm.; *in situ* widely dilated to the right. The organ is fairly firm; musculature shows some bronzing. Subepicardial fat is excessive in the usual situations. There are small epicardial plaques. The left ventricle is firm; the wall measures 2 cm.; the cavity is small. The aortic orifice measures 9 cm.; valve leaflets are thickened at the bases. The anterior leaflet in the sinuses of Valsalva has calcareous plaque-like thickenings. The mitral orifice measures 11 cm.; the valve leaflets are moderately thickened throughout, also toward the base. The chordæ tendineæ are lengthened, but are thick; papillary muscles are short and stocky. The heart cavities contain stratified chicken-fat clot. The right ventricular wall measures 7 mm.; tricuspid orifice, 10 cm.; the valve leaflets are thin; pulmonary orifice measures 11 cm.; the valve leaflets are thin.

Aorta. Retains some of its elasticity; shows upon the intimal surface various yellowish platelets.

MICROSCOPICAL. *Lung*. The pleura on these sections is thin. The alveolar spaces have in one section become quite thin and stretched so that the spaces were dilated. Upon this, due to pressure of the pleural fluid the spaces were compressed so that now most of the section shows the wall in apposition. To overcome this the emphysema has remained in a compensatory way in other parts, mostly in the periphery of the lung. Congestion is quite marked, and this is probably passive in nature, due to large numbers of heart-failure cells. The bronchi have well-developed catarrhal effects, in that the epithelial cells were proliferated then swollen and many desquamated, so that the bronchial lumina are filled with mucus and débris. The bloodvessel walls are quite thick, owing to old fibrous tissue.

The second section has been taken from a point where pressure of the fluid was of longer duration. Here some cellular proliferation, with organization of fibrous tissue, is taking place in some of the walls of the compressed air spaces.

Heart. The epicardium on the section is thin. The subepicardial fat is moderate. The coronary vessels are quite thick and slightly congested. There is no increase to the connective tissue except about some of the vessels. The endocardium, however, is quite thick, showing penetration into the myocardium between the pectinate muscles. The myocardium shows evidences of an old hypertrophy, since here and there a clear division is well shown. At present an atrophy overshadows the increase in size. This is manifested by a thinning of the fibers with the deposition of considerable myohemoglobin at the poles of the nuclei. There are no marked degenerative features.

Aorta. Arteriosclerotic changes are moderate, mostly confined to the intima. The latter has many thickenings; loss of elastica is prominent; replacement by fibrous tissue with secondary hyalinization is confined to patches. Here also a patchy fatty change has taken place in the intima.

Liver. The capsule of Glisson is not thickened, although some cellular proliferation is to be seen in perilobular positions. No marked proliferation is present. The central lobular veins are slightly dilated and filled with red blood cells, which congestion extends into the capillaries. The liver cells show well-marked degenerative changes, more so about the central lobular veins. Here the cells are broken down, outlines poor, granular and filled with multiple small vacuoles. Many of those just about the rim contain fine brown granular pigment.

Spleen. The capsule is decidedly thickened and irregular. The trabeculæ are not prominent. The bloodvessel walls show some hyaline change. The follicles are loose and open. The general splenic pulp is loose and the small cells are present without any definite hyperplasia. Congestion is moderate and there is no pigment.

Pancreas. There are no prominent fibrous-tissue changes. The parenchymal cells take the stain well and are compact. The islands of Langerhans are also small and compact. There has been some atrophy, as evidenced by replacement by a considerable amount of fat.

Kidneys. The capsule is not thickened, but in places there is some proliferation into the cortex. The fibrous tissue is not prominent, although very slightly increased. The bloodvessels are rather prominently congested. The glomerules are full; there is swelling due both to proliferation plus congestion and distention of spaces. The tubular cells are small and very granular, and their nuclei are sharp; granular casts predominate. The usual fibrous stroma is present in the medulla. The other section is like its fellow, except that degeneration of the cortical tubules is more prominent.

Adrenals. Capsule and fibrous tissue are not marked. The parenchymal cells are open and separated probably by fluid. The cells show both granules and vacuoles in equal number. Medullary congestion is moderate; chromophilic proliferation of medullary cells is not marked.

Tumor. Six slides taken from the tumor mass in the axilla, lymph nodes and pectoral muscle. The slides show the same type of tumor for all. The cell is a small round or oblong cell, with a small amount of acid-staining protoplasm and a large vesicular and hyperchromatic nucleus. It is larger than a lymphocyte and about the size of an endothelial cell. Grossly large degenerated areas are described. Microscopically these areas appear as coagulated and necrotic tumor cells which are swollen, diffusely acid staining, with complete loss of nuclei. In the active portion of the slides karyokinetic figures are well seen.

Bacteriological Examination. Tubercle bacilli were not found. Streptococcus was found in cultures from the heart blood, lung, spleen, liver, kidney and lymph nodes of the neck.

These three cases, while finally diagnosed in Case III as sarcoma and in the others as aleukemic leukemia, nevertheless present many features in common. They illustrate first how these cases may remain for many months without seriously disturbing the patient's general health, so that they are incorrectly diagnosed, or temporization is practised until the entire lymphatic system is involved beyond reasonable expectation of good result. All three cases died from intercurrent acute infection after a short and rather stormy course.

All of them were at first supposed to be Reed-Hodgkin's disease, but certain clinical features stamped them as atypical if they were to be so classified. The ages—sixty, sixty-one and sixty-one—are twice the average of our own cases of lymphogranuloma. Cases I and II from the history showed that there had been an extensive involvement of the lymphatic apparatus from almost the very beginning. This was a point against the diagnosis of Hodgkin's disease, as it practically always begins as a localized process, and extends usually from one group to another until it has become more or less generalized. It is the exception rather than the rule for cases of Hodgkin's disease to show extensive involvement of all the superficial lymphatic groups. Theoretically it would eventually do so, but death usually frees the patient before this has occurred. On the other hand leukemia, both of the leukemic and aleukemic type, is essentially a general disease. One group of glands, it is true, may be much larger than another, but the enlargement of the whole system is always discoverable. In the ever-varying clinical manifestations of individual patients it may be difficult to establish with certainty that most or all lymph nodes became enlarged at or near the same time. The fact that the adenopathy is general is quite as important as the uniformity and synchronism of the enlargements. Patient history-taking and physical examination will aid greatly, but the histology of an excised gland will clinch the matter. This is illustrated in Case III, which was diagnosed by biopsy as sarcoma. There was no special involvement of the inguinal groups, and at postmortem there was none of the abdominal glands.

In comparing the three cases clinically at the very outset the chief complaint is enlightening. The patient whose case was diagnosed as sarcoma gave as his chief complaint, "Swelling under the arms and in the neck," while the two cases of aleukemic leukemia gave as their complaints, "Swelling in the armpits, the neck and the groins" and "Swelling on both sides of the neck, in the axillæ and in the inguinal regions," respectively.

The first patient complained of a more or less localized trouble and the other two of a pretty generalized process. This distribution was borne out upon physical examination, and in the latter cases should have led the clinician to consider the leukemias rather than Hodgkin's disease or lymphosarcoma.

The small tumors appearing early above the scapulæ in the leukemic cases are unusual and suggestive. This is a point clinically against Hodgkin's disease, for while such a distribution might be possible in this condition it is more common in leukemia.

We would like to emphasize for the leukemic cases the discrete nodules in the axillæ, firm, well-outlined, movable masses, not tending to coalesce, without pain or tenderness, yet distinctly tumorous as the patient was inspected.

In leukemia the individuality, the discreteness, of lymph nodes is preserved, a condition the more readily appreciated if one consider the essence of the disease, a lymphatic hyperplasia, lacking the inflammatory character of lymphogranuloma and the disregard of the capsule by sarcoma. In Case III, however, the tumors, especially in the axillæ, were conglomerate and fixed to the subcutaneous tissue, somewhat painful and tender, with bronzing of the overlying skin, induration and some retraction of the nipple.

In many cases of Hodgkin's disease and of widespread extraneous tumors of the lymphatic apparatus other than the leukemias there occurs a reduction, in the differential count, of the mononuclear elements while the total count may remain normal or show a leukopenia. To state it figuratively there is a reduced output from the mononuclear factory because so much of it is not in working condition. This gives oftentimes an apparent polymorphonuclear leukocytosis. In the two cases of aleukemic leukemia the blood picture was as follows: The blood in Case I was at first sublymphemic, giving a count of 13,800, with small mononuclears at 36 per cent and large mononuclears at 18 per cent. Infection increased the total count and the polymorphonuclear neutrophilies. Case II had low normal total counts and very distinct lymphocytosis. On the other hand, Case III the sarcoma case, had neutrophile percentages of 86, 75 and 86, with total counts within normal limits.

In other words, from the standpoint of the clinician the two cases of aleukemic leukemia showed a blood picture which indicated activity of lymphoid tissue, a condition not found in lymphogranuloma or sarcoma.

The absence of actual leukemia does not exclude these cases from the leukemias, since Paltauf, Kundrat, Sternberg, Warthin, Fraenkel and others admit the fact that such cases may become frankly leukemic. Fraenkel maintains that if blood formulæ be followed carefully true leukemic phases may be discovered, and that he has repeatedly seen this happen shortly ante mortem.

The spleens of the two cases of aleukemic leukemia were slightly enlarged. One was found at autopsy in a state of active mononuclear hyperplasia.

There was in histological preparations from the autopsy of the first case general infiltration of organs with the mononuclear type cell and none at all in the third case. This probably more than any other feature stamps the first case as leukemia of the aleukemic type.

Relation to Cellular Hodgkins. Microscopically the pathological picture of aleukemic leukemia is widely separated from Hodgkin's disease. While the cellular type of the latter may approach the picture of uniformity of cell proliferation seen in aleukemic or leukemic growth, there are, however, always present the signs of inflammatory reaction; the large endothelioid cell and other chronic granulomatous elements are present to a greater or less extent in every case. The picture seen in leukemia, with and without an increase of circulating leukocytes, is that of a uniform cellular hyperplasia, with little or no stroma and only occasional endothelial and reticulum cells. Incidental inflammation may add granulation tissue, or under roentgen-ray stimulation large endothelioid cells may become slightly more numerous, but they do not occur in groups and the development does not approach the picture of malignant granuloma in the formation of coarse fibrous reticulum. (Contrast Figs. 1, 2 and 4 with Fig. 3.)

Careful study of the cases, bearing in mind the features discussed above will greatly aid in an early diagnosis, but it would seem that a diagnostic excision of a lymph node is the best method of making a decision, an opinion also expressed by Harvier.* Not only does this place a case in a definite group, but it gives the roentgenologist the necessary guide for treatment. This applies especially to Hodgkin's disease (lymphogranuloma malignum), which we have divided in our study into the cellular, the fibrocellular and the sclerosing varieties or stages, with the hope of learning something about the recognized fact that some cases do well with the roentgen-ray, others do badly, while still others do well for a short time only to have serious remissions. These varieties are due somewhat to the rate of growth or stages of the disease as Longcope points out, but it is to be hoped that such a working classification will in the future indicate some difference of virus or reaction of the patient. We are not now prepared to draw absolute conclusions, but it appears that in order of favorable response to roentgen-ray treatment the cases may be grouped first as most favorable, the cellular variety, second the fibrocellular and least favorable the sclerosing type. Perhaps our present information should only allow us to state that a case is favorable to the degree that it remains cellular in histology, unfavorable to the degree that it develops fibrous tumors.

The two cases of aleukemic leukemia are further interesting from the standpoint of treatment and prognosis. In Case II no treatment had been given but Case I was doing well in that no reactions had occurred, the gland masses were slightly smaller and the general health of the man was excellent. Since careful treatment of leukemic adenopathy offers definite hope in prolonging life at least, these cases should be diagnosed as early as possible, and this seems only practicable by adenectomy. We have discussed in a recent article the precautions to be used in selecting a gland for diagnostic excision.[10]

We wish to put on record a brief note of two attempts at further classification and diagnosis of these conditions that resulted negatively. Having seen that a very definitely different response to the rays was given by the cellular and fibrous groups of lymphogranuloma, it suggested itself to us that in the process of tissue destruction some specific protein might be formed and that some reactive substance might be elaborated. We were aware that the body does not produce antibodies against its own tissues, but we thought an antigen might be developed in glands under the roentgen-ray. We obtained by operation on Reed-Hodgkin's disease a large gland, from autopsy on S. O., a retroperitoneal mass, and by operation a sarcoma of the cervical glands. The first was ground in saline under sterile precautions and 0.3 per cent trikresol added. The other two were extracted according to the method of purifying proteins for skin sensitization tests. These substances served as antigen for skin tests upon the following cases:

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* La médecine, 1920.

Malignant granuloma—one case before and after roentgen-ray treatment; malignant granuloma—one case before roentgen-ray treatment; malignant granuloma—one case after roentgen-ray treatment; lymphatic leukemia—one case before and after roentgen-ray treatment.

All of these tests were negative.

Summary. 1. Two cases of aleukemic leukemia and one case of lymphosarcoma, similar, to some degree, in clinical course and physical appearance, and their distinction from lymphogranuloma, are reported.

2. Attention is called to the need for classification of the enlargement of lymphatic bodies and the hyperplasias of these and allied tissues in the absence of a definite increase in the circulating leukocytes.

3. The term "pseudoleukemia" has outlived its usefulness as a noun and should be used in an adjectival sense only.

4. Aleukemic leukemia is a systemic lymph-tissue disease, in pathology essentially like typical leukemia, but without increased circulating leukocytes. Leukemic phases may occur in its course or just ante mortem. (Compare Figs. 1, 2 and 4.)

5. A generalized lymphadenopathy is more suggestive of leukemia than of lymphogranuloma and tumors.

6. The two cases of aleukemic leukemia reported, while showing very extensive involvement of the lymphatic apparatus, gave no reduction of circulating mononuclears, a relative reduction being a picture usually seen in granulomata and sarcomata, involving much of the lymphatic apparatus. This point should be a decided help in clinical differential diagnosis.

7. Aleukemic leukemia is widely separated from cellular Hodgkin's disease in its histology by the absence of inflammatory changes in the former and their presence in the latter; leukemic processes are definitely more uniform or homogeneous than granulomatous.

8. An excision of a lymph node for microscopic study is the only reliable method of making a decision as to diagnosis in lymphatic enlargements. It is valuable also from the standpoint of prognosis and treatment.

9. Mention is made of a difference in the response to the roentgen-ray of the leukemic and the granuloma groups as seen in the affected lymph node. This will be taken up in a later communication.

10. An attempt at the production of an antigen for specific protein skin tests in the lymphatic diseases resulted negatively.

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THE HEART IN INFECTIOUS DISEASE.[1]

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One of the most interesting and puzzling questions in the practice of medicine is the effect of infectious disease on the heart. Much unwarranted empiricism still exists in the treatment of the circulation during and after an infection. It is well now and again to pause and to take account of the progress of our knowledge of the influence of infectious disease on the heart and circulation. It is my desire to call attention to some of the known facts of this influence and to urge investigation of points that are in doubt. I shall take up in turn briefly the pathology, symptomatology and treatment of the heart in infectious disease.

In discussing the changes in the heart due to infections it is necessary to separate these infections into two groups: First there are those diseases which are quite likely to cause some permanent damage to the heart, and, second, there are infectious diseases in general which poison the heart temporarily but probably result in little or no permanent damage. In the former group are, in the first place, the infections of the rheumatic type—rheumatic fever, chorea, tonsillitis and scarlatina; secondly, there is diphtheria; thirdly, syphilis; and finally, the diseases, such as pneumonia, influenza and streptococcus septicemia, which may rarely attack the

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[1] Read before the Section on General Medicine of the College of Physicians of Philadelphia, March 28, 1921.